UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,957	02/03/2005	Jonathan S. Stamler	STAM3002 PCT	6780

23364 7590 08/14/2007

BACON & THOMAS, PLLC
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	**PAPER NUMBER**
1618	
MAIL DATE	**DELIVERY MODE**
08/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,957	STAMLER ET AL.	
	Examiner	Art Unit	
	GiGi Huang	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *1-24 and 42-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/10/2004 and 08/18/2006.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group V, claims 35-41 in the reply filed on May 14, 2007 is acknowledged.

2. Claims 1-34 and 42-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 14, 2007. Applicant's request and arguments to combine Groups IV and V has been considered and are not persuasive. The restriction is thereby made FINAL.

Status of Application

3. Claims 35-41 are present for examination at this time.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are directed to treating a patient in

need of nitroglycerin therapy. Such a method requires treatment of unspecified disease or disorders and there is no evidence indicating that the applicant knew all treatable diseases or disorders. Therefore, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

The claims are also drawn to a "mitochondria selective" dithiol and a "reductant capable of activating mtALDH". A "mitochondria selective" dithiol is defined on Page 12 in the specification is a dithiol that has the "ability to access mitochondria more readily than other cell components". The description is inadequate to one of skill in the art to distinguish what the inventors were in possession of at the time of filing.

First, claims and description define the thiol by what it *does* and not what it *is*. Second, it does not describe adequately the degree of access or permeability to mitochondria or what specific dithiols would fulfill the description. As a result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

The definition of "reductant" is a "reducing agent" (Page 11). The term "capable of activating mtALDH" is "capable of reducing oxidized mtALDH so the enzyme can catalyze conversion of GTN to 1,2-GDN". The reductants must cause "at least 20% 1,2-GDN formation" to be considered (Page 11). The description is inadequate to one of skill in the art to distinguish what the inventors were in possession of at the time of filing.

First, the claims and description define the reductant by what it *does* and not what it *is*. Second, it describes the reductant through a measurement of enzyme production. This does not adequately describe which reductant is addressed as it is inadequate to describe a product to be administered through the function of another

mechanism, such as enzyme efficiency which can be affected by many conditions like temperature (e.g. fever) not related to the invention. As a result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

As only dithiothreitol (DTT), dihydrolipoic acid (DHLA) and tris(2-carboxyethylphosphine) are exemplified in Page 37, Background Example 4, only that reductants and dithiols and are to be considered.

Claims 35-41 are rejected.

Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for *every* coronary syndrome and condition, restenosis, asthma, or rectal spasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant has reasonably demonstrated that the specific dithiols: dithiothreitol (DTT), dihydrolipoic acid (DHLA) and tris(2-carboxyethylphosphine), are useful as a therapeutic agent for delaying, postponing, and/or reducing nitroglycerin tolerance in angina. However, the claims also encompass using the claimed compound to prevent or reverse nitroglycerin tolerance which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" or "reverse" is an absolute definition which means to stop from occurring or to create a situation where the episode never happened, and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the

medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented or completely reversed with current therapies (other than certain vaccination regimes) – including preventing such disorders as myocardial infarcts, which is clearly not recognized in the medical art as being a totally preventable condition.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to *every* unstable coronary condition, restinosis, asthma, and rectal spasms. Thus, the claims taken together with the specification imply the invention is capable of addressing each and every one of these conditions.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art shows that nitroglycerin is currently advised for use in angina but the benefits with or congestive heart failure have not been established to date, and are contraindicated in acute myocardial infarction, constrictive pericarditis,

and pericardial tamponade (see Physician Desk Reference pages). As taught by Kennedy et al. (Airway response to sublingual nitroglycerin in acute asthma, JAMA), nitroglycerin was inadequate for the treatment of acute asthma and did not significantly change neither the forced expiratory volume nor the forced vital capacity of air for those tested showing that nitroglycerines in not adequate initial therapy for asthmatic attacks, in fact he teaches that its use could be dangerous. The unpredictability for the drug in the art is high and it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug, resulting in an unclear expectation of what would be successful.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance solely for angina in Examples XXXII and XXXIII.

However, the specification does not provide for all other unstable coronary condition, restinosis, asthma, and rectal spasms.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the high degree of unpredictability in the art for nitroglycerin, it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug. Without experimentation, as

currently claimed, the scope of the invention would require undue experimentation of one skilled in the art to address each and every condition and every combination without a clear expectation of success.

As evidenced therein, along with the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claims 35-41 are rejected.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate).

It is noted that the translation provided is a machine translation from the European Patent Office and for clarity "alpha Liposaure" is alpha-lipoic acid and "Glyceroltrinitrate" is nitroglycerin.

Weischer teaches the combination of alpha-lipoic acid (enantiomers, derivatives or metabolites) and organic nitrates, including nitroglycerin in combination preparation. He teaches that the combination showed a greater anti-ischemic effect than when the nitroglycerin was administered alone. Thereby the combination of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) showed a therapeutic anti-organic nitrate tolerance effect. There were in vitro and in vivo models performed. The in vivo models were comprised of administering by balloon catheter to animals (dog and house pig) with follow up histological investigation. The combination is envisioned for angina pectoris among other conditions. Weischer teaches the composition and methods of administration for angina with humans (see DE 4420102, Page 6, Table 1). Weischer goes on to claim the method of use in Claim 21 (citations are based on the translation provided – Specification: Page 1, paragraphs 1, 7, 9, 16-17 of 19 on page, Page 2, paragraphs 2-9 of 18 on page, Page 4, paragraph 2-10 of 28 on page, Page 6, paragraph 10-14 of 21 on page, Page 7, paragraph 14 of23 on page, Claim set: Page 2, claim 21).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 35-38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy (Influence of redox compounds on nitrovasodilator-induced relaxations of rat coronary arteries, British Journal of Pharmacology) in view of Laursen et al. (In Vivo Nitrate Tolerance Is Not Associated With Reduced Bioconversion of Nitroglycerin to Nitric Oxide, Circulation).

Murphy teaches use of six redox compounds to test for their influence on nitrovasodilation.

The six redox compounds including dithiothreitol (DTT) - a dithiol reductant and ferricyanide - an anionic oxidant.

Murphy teaches that the relaxation profiles suggested two pathways by which nitroglycerin-released nitric oxide. There was a loss in sensitivity to nitroglycerin over time (tolerance) in the control and in some of the redox compounds. However, DTT preserved the initial relaxation even through the fourth nitroglycerin protocol (resisted and delayed tolerance). Ferricyanide in contrast attenuated the initial relaxation during the first protocol. This taught that DTT preserves the process promoting nitric oxide release from nitroglycerin while the oxidant eliminated it. Murphy taught that tolerance would be by delayed with the use of a high-affinity, labile reductant or a low affinity reductant not glutathione.

Murphy does not expressly teach the administration of the dithiol and reductants to a patient.

Laursen et al. teaches the process of where in vitro data suggesting reduced bioconversion of nitroglycerin to nitric oxide contributed to nitroglycerin tolerance led to in vivo studies.

Laursen teaches that the next step after in vitro studies was to examine the in vivo validity of the hypothesis by measuring the nitroglycerin derived nitric oxide formation in a patient (rats). This was done with catherization of the rats. The study showed that tolerance is not associated with the in vivo bioconversion of the nitroglycerin to nitric oxide, but most likely from a substance derived form the endothelium (Abstract, Page 2, Introduction, Page 3, Methods- Animals section, Induction of Nitrate Tolerance section, Page 5, Experimental Protocols section-study 1, Page 6, Study2-3, Page 10, Discussion section, Page 11-12)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to formulated an in vivo study after an in vitro study, as suggested by Laursen, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it would be the natural progression for the development of any drug. There is lab testing, animal model testing and administration, human short-term clinical trials, long-term human clinical trials, and FDA approval, to reach mass manufacture for the market place.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

All the critical elements are taught by the cited reference and thus the claims are rejected.

9. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation, Abstract only).

The teachings of Murphy in view of Laursen et al. are is discussed above especially the fact that Murphy taught that tolerance would be by delayed with the use of a high-affinity, labile reductant or a low affinity reductant that was not glutathione.

Murphy in view of Laursen et al. does not expressly teach the use dihydrolipoic acid.

Prugin et al. teaches that dihydrolipoic acid is an effective thiol, especially as a reducing agent. It was tested along with dithiothreitol (DTT) and glutathione in the presence of thiol-alkylating agents. DTT and dihydrolipoic acid were able to reverse the inhibition of the alkylating agents to various degrees. Glutathione however was not able to reverse the inhibitory effects. Reactivation of microsomal ATPase by the dihydrolipoic acid was mostly the reason for its protective effect on peroxidation making it an obvious

choice for the incorporation in the teachings of Murphy in view of Laursen as a labile reductant that was not glutathione (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize dihydrolipoic acid, as suggested by Prugin, and produce the instant invention. As suggested by Murphy in view of Laursen, a high-affinity, labile reductant or a low affinity reductant that was not glutathione would be desirable to defer nitroglycerin tolerance.

Thereby, one of skill in the art would search for analogous or effective reductants in similar capacities to combine with the nitroglycerin. Prugin taught the dihydrolipoic acid is an effective thiol, especially as a reducing agent. One of skill in the art at the time would utilize dihydrolipoic acid as it has many reductant and protective properties, especially its in light of its ability to overcome inhibition in comparison to glutathione.

One of ordinary skill in the art would have been motivated to do this because dihydrolipoic acid is naturally found in the body so it as it would mostly likely not have negative side effects compared to other available reductants.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. It is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

All the critical elements are taught by the cited reference and thus the claims are rejected.

10. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Getz et al. (A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry, Analytical Biochemistry).

The teachings of Murphy in view of Laursen et al. are discussed above.

Murphy in view of Laursen et al. does not expressly teach the use of tris(2-carboxyethyl)phosphine.

Getz et al. teaches that the sulfydryl reductant tris(2-carboxyethyl)phosphine (TCEP) is an attractive alternative to commonly used dithiothreitol (DTT). The reductants preserve enzymatic activity that is sensitive to sulhydryl oxidation equally. However, TCEP is desirable because it is more stable than DTT especially for long-term storage wherein DTT would require metal chelates in the buffer for preservation.

TCEP is noncompetitive with protein sulfydryls for attachment of thiol-reactive dyes giving TCEP a major advantage over DTT. Getz concluded that TCEP had clear advantages over DTT, and thereby preferable, but the choice of reductant is application specific (Abstract, Page 73, 2nd column, Page 74, 1st column, Page 80).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute tris(2-carboxyethyl)phosphine for DTT, as suggested by Getz, and produce the instant invention. One of skill in the art at the time would utilize tris(2-carboxyethyl)phosphine as it has many advantages over DTT, especially its stability for testing, administration, and manufacture.

One of ordinary skill in the art would have been motivated to do this because tris(2-carboxyethyl)phosphine is especially stable over DTT, particularly with out the presence of a metal chelates. Stability is critical for any drug for storage, administration, and manufacture. The fact that an additional ingredient is not required for stability reduces costs, increases storage time, and the duration of use of the drug to be administered.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. It is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

All the critical elements are taught by the cited reference and thus the claims are rejected.

Conclusion

11. Claims 35-41 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GiGi Huang whose telephone number is (571) 272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH

ZOHREH FAY
PRIMARY EXAMINER
GROUP 1600

Zohreh Fay